Case reports

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Candida endocarditis in a premature infant

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1 Introduction

Invasive candidal infections in the neonatal period have been increasing steadily during the past decade [3, 8, 12]. The increase of invasive candidal infections in newborn infants can at least in part be attributed to increased survival of premature infants as a result of technological advances in neonatal care [1]. Endocarditis is an uncommon complication of invasive candidiasis. We will report the development of candidal endocarditis in a very low birth weight infant, even after antifungal therapy had been administered.

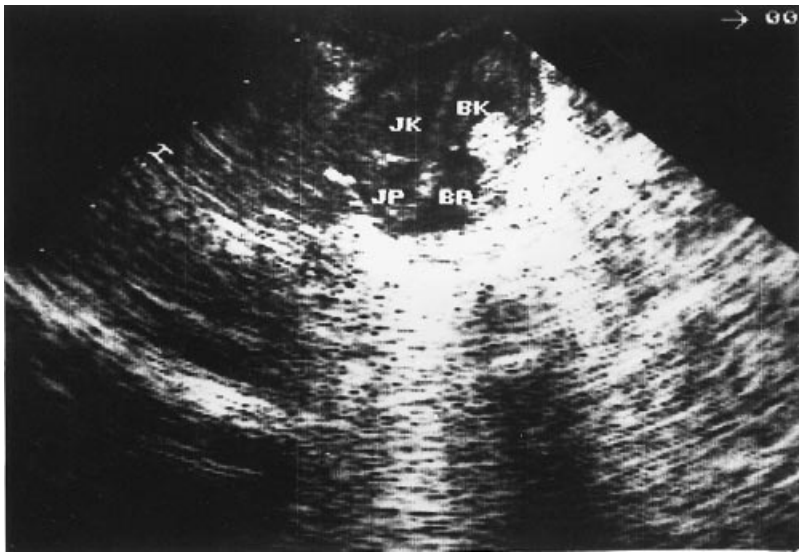
2 Case report

This 780-g male infant was delivered vaginally in an ambulance car at an unknown gestational age to a 23-year-old mother. On arrival at the neonatal intensive care unit he required complete resuscitation. Mechanical ventilation was started because of respiratory distress syndrome. An umbilical arterial catheter was inserted to the level of the diaphragm and remained in place for 8 days. Besides a dopamine and dobutamine infusion, ampicillin/sulbactam and netromycine were also administered for 17 days.

A Grade III intracranial hemorrhage was detected with a cranial ultrasound. Nose and throat cultures were obtained on day 1 and Klebsiella and coagulase negative Staphylococcus were isolated. On day 8 the infant developed symptomatic patent ductus arteriosus, which required intravenous indomethacin therapy. On the following day the closure of the ductus arteriosus was documented by an echocardiograph. On day 12, he was extubated but still required nasal CPAP therapy. On day 18, the infant developed abdominal distension. The white blood cell count was 26×10^9/L, while the platelet count was 87×10^9/L. The CRP value was 56 mg/L. Echocardiography did not show vegetation or any structural anomaly except for patent foramen ovale at this time. Cultures were obtained from nose, throat, stool and cerebrospinal fluid. Cultures from blood were not obtained because of technical difficulties. The increase in the frequency of invasive candidal infections had not been experienced in our department previously. Owing to this, bacterial infection was suspected and the infant was treated with ceftazidim until the results of the cultures arrived. Candida albicans was isolated from each culture. Parenteral fluconazol therapy was initiated on day 25 at a daily dose of 3 mg/kg. Five days later repeated cultures remained sterile except for the cerebrospinal fluid. Intravenous fluconazole therapy was continued. On day 40 a loud systolic murmur was detected. Echocardiography demonstrated a 6×7 mm pedunculated mass in the left atrium that prolapsed into the left ventricle (figure 1). Another mass was detected in the right ventricular outflow tract spreading into the pulmonary artery causing remarkable narrowing of the pulmonary artery (figure 1). Surgical removal of the vegetations was not recommended because of the very low body weight and severe state of the infant. Finally, the patient received higher doses of fluconazole, but he deteriorated rapidly and died on day 45.

During autopsy, we found both macroscopic and microscopic features of immaturity. However, no

morphologic signs of congenital malformations in any of the major organs were found on the newborn. The brain showed mild edema and hydrocephalus with posthemorrhagic and infarcted periventricular lesions. Light microscopy showed, that the alveolar spaces of the lungs had not been expanded completely and had contained eosinophilic proteineous precipitates characteristic of hyaline membrane disease. In addition, focally massive intraalveolar and interstitial hemorrhages with interstitial pneumonitis were also demonstrable. In some of the pulmonary and cerebral



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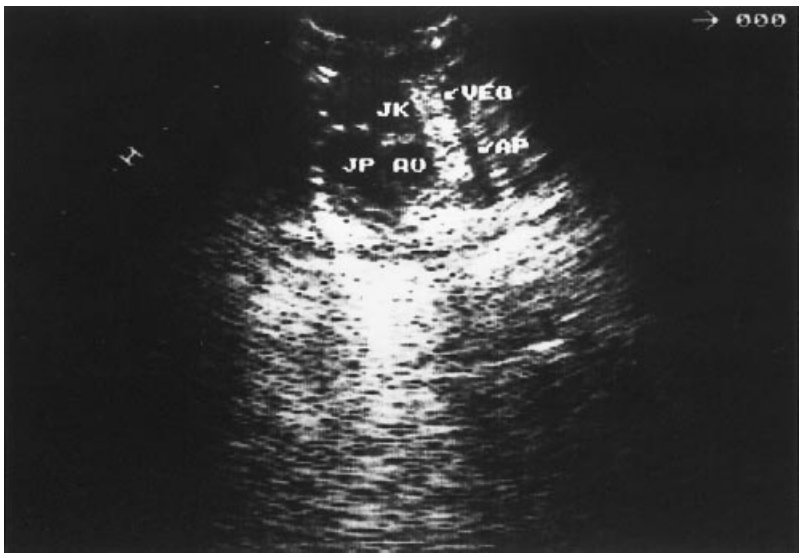

B

Figure 1. The transthoracic echocardiography: **A** − The four-chamber view, showing a large pedunculated mass attached to the left atrial wall and prolapsing into the left ventricle **(**BK: left ventricle, BP: left atrium JP: right atrium, JK: right ventricle**). B** − The parasternal short axis view: a fungal mass narrowing the right ventricular outflow tract (JP: right atrium, JK: right ventricle, AO: aortic root, AP: pulmonary artery, VEG: vegetation).

vessels fungal and bacterial embolic colonies were present indicating sepsis (figure 2). Furthermore, the heart was found in a normal anatomic position without signs of congenital heart defect. However, bulky vegetations were present on the mitral valves obscuring the valve leaflets. Accordingly, the endocardium and the subendocardial myocardium showed fibrin-rich destructive inflammatory leukocytic infiltrates that contained colonies of PAS-positive Candida albicans (figure 2). There were no signs of necrotizing enterocolitis.

3 Discussion

The frequency of candidal blood stream infections has increased by as much as 20-fold in some

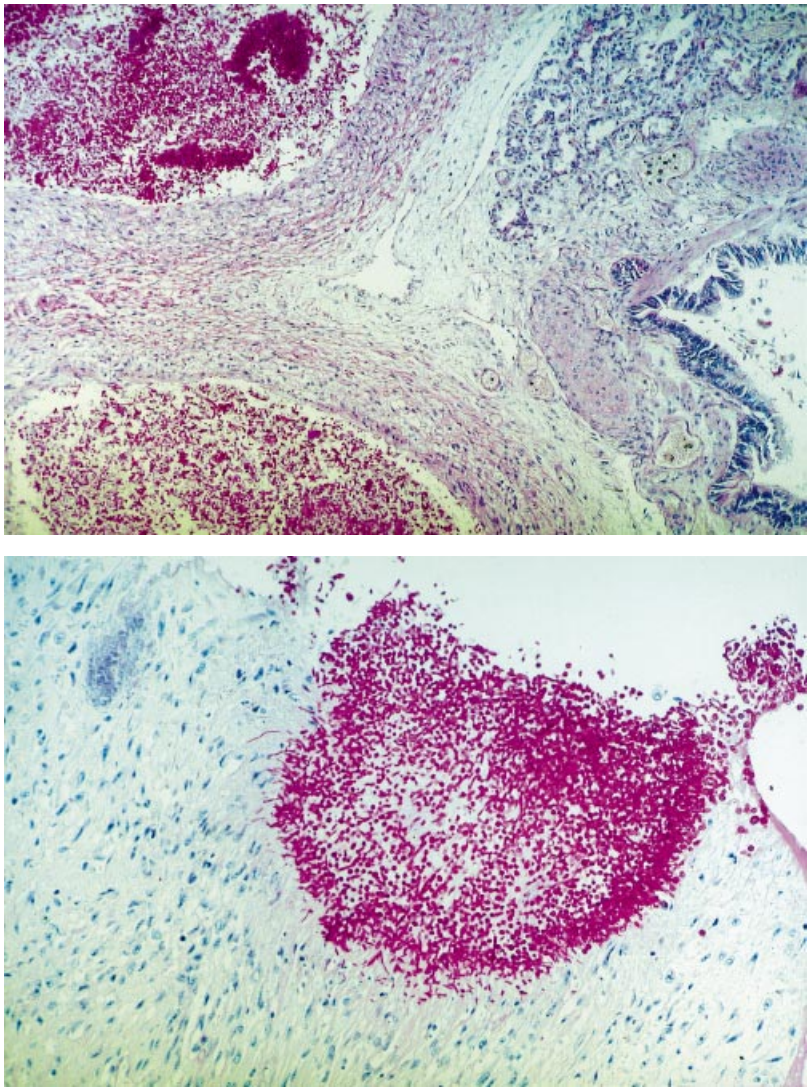

Figure 2. **A** − Autopsy lung specimen: PAS staining reveals intravascular PAS-positive embolic colonies indicating fungal sepsis. **B** − Autopsy heart specimen: PAS staining reveals intracardiac fungal vegetation destroying endocardium and spreading into the subendocardial myocardium.

institutions [4]. Premature neonates hospitalised in neonatal intensive care units are particularly prone to infection by Candida species, especially albicans. Prolonged antibiotic therapy, intubation, intravenous catheterization, parenteral nutrition and corticoid therapy can all contribute to this susceptibility [1, 3]. Lymphocytes from premature infants, especially from male infants, have reduced capacity to inhibit the growth of C. albicans [14]. Phagocytosis of Candida albicans by leukocytes in premature and mature infants has been shown to be similar to phagocytosis in adults [17]. On the other hand the cytotoxic activity of neonatal macrophages cannot be fully activated by IFN-gamma [10]. The increased survival and prolonged stay in intensive care for small premature infants has resulted in a higher workload for nurses, which can lead to a breakdown in asepsis during child handling [2]. This phenomenon has been demonstrated previously during bacterial infections [5]. The increased need for neonatal beds and personnel has not been accompanied by the recruitment of more nurses and doctors during the past few years in Hungary.

Prolonged treatment with antibiotics probably played a role in the development of systemic fungal infection in our patient.

We chose fluconazole for the treatment of systemic candidiasis in order to avoid the toxic effects of amphotericin B and flucytosine. Fluconazole had only a transient effect and could not control the progression of the disease. Similar observations have been reported in candidemia occurring in infants [8]. The development of Candida endocarditis in a premature infant while being treated with fluconazole had not previously been reported. Candida endocarditis is a relatively rare complication of invasive candidiasis, but it may represent the tip of the iceberg concerning fungal infections.

Most cases of fungal endocarditis in early infancy are associated with central venous catheterization. 17 premature infants have previously been described with fungal endocarditis [11]. In 15 cases the use of a central venous catheter was reported. In our patient an umbilical arterial catheter was inserted for 8 days and thereafter the peripheral veins were cannulated. Although the umbilical arterial catheter was removed ten days before the symptoms appeared, it might have been a contributing factor in the development of the systemic fungal infection. No structural heart anomalies were detected by echocardiography and autopsy. Transient symptomatic ductus arteriosus was treated successfully with indomethacin. Experimental work with animal models has demonstrated that damaged endocardium or prosthetic material can serve as foci for the localisation of candidal infection in fungal endocarditis [9, 16]. In our case, none of the mentioned factors were observed. It is very likely, vegetations can develop without previous mechanic endothelial damage.

Echocardiography is a valuable diagnostic tool in the case of fungal endocarditis [6]. Echocardiography alone cannot distinguish infected from noninfected lesions, but the clinical course, persistent fungemia will confirm the diagnosis. A combined medical and surgical approach is required in the case of fungal endocarditis [6, 7, 15], although successful medical management has also been reported [13, 18]. In critically ill infants antifungal therapy without surgery may be an option because of the high rates of perioperative mortality [13, 18]. In our case surgical intervention was not applicable because of the size and severe condition of the baby. Because of the well-known nephrotoxicity of amphotericin, we preferred fluconazole treatment. The question arises whether an exchange of fluconazole treatment into the amphotericin infusions would have resulted in a favorable outcome. Increased awareness of Candida endocarditis should have prompted an earlier echocardiographic investigation even if no cardiac symptoms had been present [6].

The aim of this report is to emphasize the high risk of the development of fungal infections in very low birth weight infants being treated with antibiotics. As soon as clinical signs of infection appear during or very shortly after a certain period of antibacterial therapy, also systemic antifungal treatment should be initiated immediately after obtaining cultures. Furthermore, echocardiographic evaluation during antifungal treatment should be recommended.

Abstract

Endocarditis is an uncommon complication of invasive candidiasis. We present a fatal case of endocarditis caused by Candida albicans in a very low birth weight infant. The 780-g male infant did not have any structural heart disease and a central venous catheter was not placed. Endocarditis developed in spite of parenteral fluconazole treatment. Echocardiography was a valuable tool in making the diagnosis. The infant died on the 40th day of life. The development of Candida endocarditis in a premature infant who was treated with fluconazole had not been previously reported. In the case of systemic candidiasis, premature infants require very careful monitoring for the progression of the disease, even if antifungal therapy is administered.

Keywords: Candida albicans, endocarditis, premature infant.

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